AMENDMENT

In the specification:

Please amend the title to read as follows:

Human *Notch* Ligand Proteins and Polynucleotides Encoding the Same

RESPONSE

I. Status of the Claims

Claims 1-8 are presently pending in the case.

II. Objections

The Action objects to the use of the term "Novel" in the title. The title as amended is believed to have successfully addressed this issue.

III. Rejection of Claims Under 35 U.S.C. § 101

The Final Action rejects claims 1-8 under 35 U.S.C. § 101, as allegedly lacking a patentable utility due to not being supported by a specific, substantial, and credible utility or, in the alternative, a well-established utility. Applicants respectfully traverse.

The Final Action disagrees with Applicants' logical assertion, based on the evidence, that the sequences of the present invention encodes novel members of the *Notch* ligand family. In the previous response, Applicants have provided several pieces of evidence that those of skill in the art would find Applicants' assertion credible and that the utility of Notch ligands is well established and known to those of skill in the art.

The Action cites Yan et al. ("Yan"; 2000, Science 290:523-527) for the proposition that a protein's membership in a particular family does not nessicarily predict a function (Action at page 4 line 4). However, this paper cites only one example, two isoforms of the anhidrotic ectodermal dysplasia (EDA) gene, where a two amino acid change conforms one isoform (EDA-A1) into the second isoform (EDA-A2). While it is true that this amino acid change results in binding to different receptors, it is important to note, however, that the different receptors bound by the two isoforms are in fact related

(Yan at page 523). Furthermore, the EDA-A2 receptor was correctly identified as a member of the tumor necrosis factor receptor superfamily based solely on sequence similarity (Yan at page 523). Thus, Yan is hardly indicative of a high level of uncertainty in assigning function based on sequence or family membership, and thus also does not support the alleged lack of utility. The action also cites a series of older articles each of which is said to support the proposition that function cannot be predicted based on structural information. It should be noted that none of these articles refer to Notch ligands. Applicants respectfully disagree and believe that those of skill in the art recognize the structure-function relationship and that this position is supported by the many references often provided by Examiners as teaching that structural homology alone is not a good predictor of function. See, for example, Ji *et al.* ("Ji":1998, J. Biol. Chem. *273*:17299-17302). Ji notes that "a substantial degree of amino acid homology is found between members of a particular subfamily" (Ji at 17299, first paragraph). This quote suggests that homology with members of a G-protein coupled receptor is indicative that the particular sequence is in fact a member of that family and supports applicants assertion that a structure-function relationship is well- established.

Included in the Action's reasons for the alleged lack of utility of the present invention is the concern that the present application contained "no working examples of any kind, only assertions" (action at page 7, lines 10-11). This emphasis is misplaced as it has long been established that "there is no statutory requirement for the disclosure of a specific example". *In re Gay*, 135 USPQ 311 (C.C.P.A. 1962). Applicants assertion of the stated utility is legally sufficient and should control the utility analysis unless the Examiner meets the burden of establishing the lack of utility by making evidence of record that conclusively refutes the Applicants asserted utility.

The Action states (Page 8, lines 3-10) that under 101 and current Utility Examination guidelines, the term "useful" has been redefined. Applicants understanding is that issued United States patents retain a legal presumption of validity which in this case indicates that the inventions claimed in the cited patents are *legally presumed* to be in full compliance with the provisions of 35 U.S.C. sections 101, 102, 103, and 112. Applicants respectfully submit that, absent a change in the law as enacted by Congress and signed by the President, it is improper for the Examiner to hold Applicants' invention to a different legal standard of patentability. Given the rapid pace of development in the biotechnology arts, it is difficult for the Applicants to understand how an invention fully disclosed and free of prior art at the time the present application was filed, could somehow retain *less* utility and be

less enabled than inventions in the cited issued U.S. patents (which were filed during a time when the level of skill in the art was clearly lower). Simply put, Applicants invention is *more* enabled and retains *at least as much* utility as the inventions described in the claims of the U.S. patents of record. Any argument to the contrary is at best arbitrary and at worst capricious. Absent authority provided by an act of Congress or Executive order, arbitrary or capricious conduct by an administrative office the U.S. government has historically proven to conflict with the provisions of the U.S. Constitution. The Patent Office does not have the authority to rewrite U.S. law. However, the Patent Office does have a Constitutional obligation to administer U.S. law in an unbiased and procedurally consistent manner. That is what the Applicants are respectfully requesting the Examiner to consider in the present matter. As the issued U.S. Patents cited above are presumed to meet all of the requirements for patentability, including 35 U.S.C. §§ 101 and 112, first paragraph, Applicants respectfully submit that the presently claimed polynucleotide must also meet the requirements of 35 U.S.C. § 101.

Given the historic legal test for utility simply involves an assessment of whether those skilled in the art would find any of the utilities described for the invention to be credible or believable, this is clear evidence that those skilled in the art would have recognized the function and activity of the protein encoded by the sequences of the present invention, there can, therefore, be no question that Applicants' asserted utility for the described sequences is "credible." According to the Examination Guidelines for the Utility Requirement, if the applicant has asserted that the claimed invention is useful for any particular purpose (i.e., it has a "specific and substantial utility") and the assertion would be considered credible by a person of ordinary skill in the art, the Examiner should not impose a rejection based on lack of utility (66 Federal Register 1098, January 5, 2001).

The Action discounts Applicants' assertion regarding the use of the presently claimed polynucleotides on DNA chips, based on the position that such a use would allegedly be generic. Applicants disagree and believe that the described polymorphisms enhance the utility of the sequences of the present invention. These polymorphisms have particular, specific utility in DNA gene chip based analysis as they have been identified to contain several coding region single nucleotide polymorphisms (cSNPs), thus increasing their utility in DNA gene chip based analysis.

As set forth in Applicants First Response, given the widespread utility of such "gene chip" methods using *public domain* gene sequence information, there can be little doubt that the use of the presently described *novel* sequences would have great utility in such DNA chip applications. The

claimed sequence provides a specific marker of the human genome (see evidence below), and that such specific markers are targets for discovering drugs that are associated with human disease. Thus, those skilled in the art would instantly recognize that the present nucleotide sequence would be an ideal, novel candidate for assessing gene expression using, for example, DNA chips, as the specification details.

Further evidence of utility of the presently claimed polynucleotide, although only one is needed to meet the requirements of 35 U.S.C. § 101 (*Raytheon v. Roper*, 220 USPQ 592 (Fed. Cir. 1983); *In re Gottlieb*, 140 USPQ 665 (CCPA 1964); *In re Malachowski*, 189 USPQ 432 (CCPA 1976); *Hoffman v. Klaus*, 9 USPQ2d 1657 (Bd. Pat. App. & Inter. 1988)), is the utility the present nucleotide sequence has a specific utility in determining the genomic structure of the corresponding human chromosome, for example mapping the protein encoding regions, as described in the specification and evidenced below. Clearly, the present polynucleotide provides exquisite specificity in localizing the specific region of the human chromosome containing the gene encoding the given polynucleotide, a utility not shared by virtually any other nucleic acid sequences (see evidence below). In fact, it is this specificity that makes this particular sequence so useful. Early gene mapping techniques relied on methods such as Giemsa staining to identify regions of chromosomes. However, such techniques produced genetic maps with a resolution of only 5 to 10 megabases, far too low to be of much help in identifying specific genes involved in disease. The skilled artisan readily appreciates the significant benefit afforded by markers that map a specific locus of the human genome, such as the present nucleic acid sequence.

Only a minor percentage of the genome actually encodes exons, which in-turn encode amino acid sequences. The presently claimed polynucleotide sequence provides biologically validated empirical data (*e.g.*, showing which sequences are transcribed, spliced, and polyadenylated) that *specifically* define that portion of the corresponding genomic locus that actually encodes exon sequence. Equally significant is that the claimed polynucleotide sequence defines how the encoded exons are actually spliced together to produce an active transcript (*i.e.*, the described sequences are useful for functionally defining exon splice-junctions). The Applicants respectfully submit that the practical scientific value of expressed, spliced, and polyadenylated mRNA sequences is readily apparent to those skilled in the relevant biological and biochemical arts. For further evidence in support of the Applicants' position, the Examiner is requested to consider the evidence provided in Applicants' previous Response. The presently claimed polynucleotide sequence defines a biologically validated

sequence that provides a unique and specific resource for mapping the genome as described in many articles.

As still further evidence supporting Applicants assertions of the specific utility of the sequences of the present invention in localizing the specific region of the human chromosome and identification of functionally active intron/exon splice junctions is the information provided in **Exhibit D**. This is the result of a blast analysis using SEQ ID NO:1 of the present invention when compared to the identified human genomic sequence. This result indicates that the sequence of the present invention is encoded by 20 exons spread non-contiguously along a region of human chromosome 20, at approximately 20p12, which are contained within partially overlapping clones, AL109657.8 and AL117333.26. Thus clearly one would not simply be able to identify the 20 protein encoding exons that make up the sequence of the present intention from within the large genomic sequence. Nor, would one be able to map the protein encoding regions identified specifically by the sequences of the present invention without knowing exactly what those specific sequences were.

For each of the foregoing reasons, Applicants submit that in light of the above discussion and those presented in previous Applicant responses, the presently claimed invention has been shown to have a substantial, specific, credible and well-established utility and that the rejection of pending claims 2, 3, 6 and 7 under 35 U.S.C. § 101 has been avoided, and respectfully request that the rejection be withdrawn.

IV. Rejection of Claims Under 35 U.S.C. § 112, First Paragraph

The Action rejects claims 1-8 under 35 U.S.C. § 112, first paragraph, since allegedly one skilled in the art would not know how to use the invention, as the invention allegedly is not supported by a specific, substantial, and credible utility or a well-established utility. Applicants respectfully traverse. Applicants submit that as the claims have been shown to have a specific, substantial, credible and well established utility, as detailed in the section above, Applicants respectfully request that the rejection of claims 1-8 under 35 U.S.C. § 112, first paragraph, be withdrawn.

V. Conclusion

The present document is a full and complete response to the Action. In conclusion, Applicants submit that, in light of the foregoing amendments and remarks, the present case is in condition for allowance, and such favorable action is respectfully requested. Should Examiner O'Hara have any questions or comments, or believe that certain amendments of the claims might serve to improve their clarity, a telephone call to the undersigned Applicants' representative is earnestly solicited.

Respectfully submitted,

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Date

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